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(54) Title: COMPOUND AND COMPOSITION FOR DELIVERING ACTIVE AGENTS

(57) Abstract: Compounds and compositions for the delivery for Parathyroid hormone are provided. Methods of administration and preparation are provided as well.

### **Compound and Composition for Delivering Active Agents**

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This application claims the benefit of U.S. Provisional Application No. 60/297,117, filed June 8, 2001, which is hereby incorporated by reference.

#### **FIELD OF THE INVENTION**

The present invention relates to compounds for delivering biologically active parathyroid hormone to a mammal. These compound are well suited for forming non-covalent mixtures with active agents for oral, pulmonary, and other routes of administration to animals. Methods for the preparation and administration of such compositions are also disclosed.

#### **BACKGROUND OF THE INVENTION**

Conventional means for delivering active agents are often severely limited by biological, chemical, and physical barriers. Typically, these barriers are imposed by the environment through which delivery occurs, the environment of the target for delivery, and/or the target itself. Biologically and chemically active agents are particularly vulnerable to such barriers.

In the delivery to animals of biologically active and chemically active pharmacological and therapeutic agents, barriers are imposed by the body. Examples of physical barriers are the skin, lipid bi-layers and various organ membranes that are relatively impermeable to certain active agents but must be traversed before reaching a target, such as the circulatory system. Chemical barriers include, but are not limited to, pH variations in the gastrointestinal (GI) tract and degrading enzymes.

These barriers are of particular significance in the design of oral delivery systems. Oral delivery of many biologically or chemically active agents would be the route of choice for administration to animals if not for biological, chemical, and physical barriers. Among the numerous agents which are not typically amenable to oral administration are biologically or chemically active peptides, such as calcitonin and insulin;

polysaccharides, and in particular mucopolysaccharides including, but not limited to, heparin; heparinoids; antibiotics; and other organic substances. These agents may be rapidly rendered ineffective or destroyed in the gastro-intestinal tract by acid hydrolysis, enzymes, and the like. In addition, the size and structure of macromolecular drugs may  
5 prohibit absorption.

Earlier methods for orally administering vulnerable pharmacological agents have relied on the co-administration of adjuvants (*e.g.*, resorcinols and non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of  
10 enzymatic inhibitors (*e.g.*, pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol) to inhibit enzymatic degradation. Liposomes have also been described as drug delivery systems for insulin and heparin. However, broad spectrum use of such drug delivery systems is precluded because: (1) the systems require toxic amounts of adjuvants or inhibitors; (2) suitable low molecular weight cargos, *i.e.* active  
15 agents, are not available; (3) the systems exhibit poor stability and inadequate shelf life; (4) the systems are difficult to manufacture; (5) the systems fail to protect the active agent (cargo); (6) the systems adversely alter the active agent; or (7) the systems fail to allow or promote absorption of the active agent.

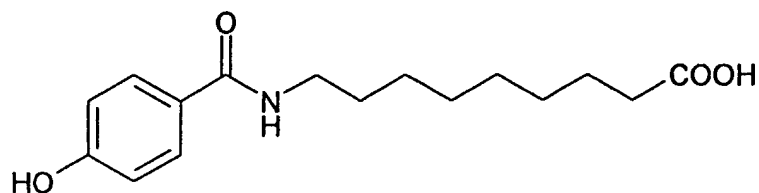
Proteinoid microspheres have been used to deliver pharmaceuticals. See, for  
20 example, US Patent Nos. 5,401,516; 5,443,841; and Re. 35,862. In addition, certain modified amino acids have been used to deliver pharmaceuticals. See, for example, US Patent Nos. 5,629,020; 5,643,957; 5,766,633; 5,776,888; 5,866,536 and International Patent Publication Nos., WO00/07979; WO0050386; WO01/132130 and WO01/132596.

More recently, a polymer has been conjugated to a modified amino acid or a  
25 derivative thereof via a linkage group to provide for polymeric delivery agents. The modified polymer may be any polymer, but preferred polymers include, but are not limited to, polyethylene glycol (PEG), and derivatives thereof. See, for example, WO 00/40203.

However, there is still a need for simple, inexpensive delivery systems which are  
30 easily prepared and which can deliver a broad range of active agents by various routes.

### **SUMMARY OF THE INVENTION**

The present invention provides compounds and compositions which facilitate the delivery of active agents. Delivery agent compounds of the present invention include those having the following formulas:



**Compound 1**

and salts thereof or mixture thereof.

The invention also provides a composition comprising at least one of the delivery agent compounds of the formulas above, and at least one active agent. These compositions deliver active agents to selected biological systems in increased or improved bioavailability of the active agent compared to administration of the active agent without the delivery agent compound.

Also provided are dosage unit forms comprising the compositions. The dosage unit may be in the form of a liquid or a solid, such as a tablet, capsule or particle, including a powder or sachet.

Another embodiment is a method for administering an active agent to an animal in need of the active agent, by administering a composition comprising at one of the delivery agent compounds of the formula above and the active agent to the animal. Preferred routes of administration include the oral, intracolonic and pulmonary routes.

Yet another embodiment is a method of treating a disease or for achieving a desired physiological effect in an animal by administering the composition of the present invention.

Yet another embodiment is a method of preparing a composition of the present invention by mixing at least one delivery agent compound of the formula above, and at least one active agent.

## **DETAILED DESCRIPTION OF THE INVENTION**

### **Delivery Agent Compounds**

The delivery agent compounds may be in the form of the carboxylic acid or salts thereof. Suitable salts include, but are not limited to, organic and inorganic salts, for example alkali-metal salts, such as sodium, potassium and lithium; alkaline-earth metal salts, such as magnesium, calcium or barium; ammonium salts; basic amino acids, such as lysine or arginine; and organic amines, such as dimethylamine or pyridine. Preferably, the salts are sodium salts. The salts may be mono- or multi-valent salts, such as monosodium salts and di-sodium salts. The salts may also be solvates, including ethanol solvates, and hydrates.

Salts of the delivery agent compounds of the present invention may be prepared by methods known in the art. For example, sodium salts may be prepared by dissolving the delivery agent compound in ethanol and adding aqueous sodium hydroxide.

In addition, poly amino acids and peptides comprising one or more of these compounds may be used.

An amino acid is any carboxylic acid having at least one free amine group and includes naturally occurring and synthetic amino acids. Poly amino acids are either peptides (which are two or more amino acids joined by a peptide bond) or are two or more amino acids linked by a bond formed by other groups which can be linked by, e.g., an ester or an anhydride linkage. Peptides can vary in length from dipeptides with two amino acids to polypeptides with several hundred amino acids. One or more of the amino acids or peptide units may be acylated or sulfonated.

The compounds described herein may be derived from amino acids and can be readily prepared from amino acids by methods within the skill of those in the art based upon the present disclosure and the methods described in WO01/44199, WO00/07979, US 6,358,504 and US 5,866,536. For example, the compounds may be prepared by reacting the single amino acid with the appropriate acylating or amine-modifying agent, which reacts with a free amino moiety present in the amino acid to form amides.

Protecting groups may be used to avoid unwanted side reactions as would be known to those skilled in the art. With regard to protecting groups, reference is made to T.W.

Greene, Protecting Groups in Organic Synthesis, Wiley, New York (1981), the disclosure of which is hereby incorporated herein by reference.

The delivery agent compound may be purified by recrystallization or by fractionation on one or more solid chromatographic supports, alone or linked in tandem. Suitable

5 recrystallization solvent systems include, but are not limited to, ethanol, water, heptane, ethyl acetate, acetonitrile, methanol, and tetrahydrofuran and mixtures thereof.

Fractionation may be performed on a suitable chromatographic support such as alumina, using methanol/n-propanol mixtures as the mobile phase; reverse phase chromatography using trifluoroacetic acid/acetonitrile mixtures as the mobile phase; and ion exchange  
10 chromatography using water or an appropriate buffer as the mobile phase. When anion exchange chromatography is performed, preferably a 0-500 mM sodium chloride gradient is employed.

Proteins and delivery agents are presumed to be transported into or through the lipid bilayers of the GI epithelial cells as a normal biological process. It is believed that  
15 the delivery agents interact non-covalently with the macromolecule to alter its physicochemical properties, for example by increasing hydrophobicity. The delivery agents were screened for their membrane interaction potential using immobilized artificial membrane (IAM) chromatography by the method of Pidgeon et al. J. Med Chem 41: 1163-1170 (1995). This *in vitro* technique, which mimics the partitioning of  
20 compounds into lipid membranes, was chosen as a model of the interaction between delivery agents and the lipophilic gastrointestinal membrane. Earlier studies in our laboratories have shown that the interaction of a delivery agent with the IAM column is a good predictor of delivery agent activity (Leone-Bay et al.: J. Controlled Release 50: 41-49 (1998). Delivery agents must transport proteins between aqueous environments  
25 through a lipophilic membrane, thus these compounds must exhibit both lipophilic and hydrophilic character. Previous studies have suggested that compounds having log relative  $k'$  values around 1 partition readily into intestinal epithelial cells (Pidgeon et al. J. Med Chem 41: 1163-1170 (1995)). To bracket this values, delivery agents having log relative  $k'$  values between 0.6 and 1.4 were selected for these studies.

30 These delivery agents, selected by IAM chromatography, were also evaluated using PTH affinity chromatography, as a model of the interaction between PTH and the

delivery agents. In this technique, PTH is covalently bound to a sepharose resin and the delivery agents are eluted through the resin-bound drug. The rate at which the delivery agents move through the column is related to the interaction with PTH. Interacting delivery agents would move through the column more slowly than non-interacting delivery agents. Thus it is proposed that active delivery agents will exhibit larger relative  $k'$  values than less active delivery agents because the more active delivery agents interact more effectively with PTH.

NMR is a sensitive tool for detecting weak interactions in exchanging systems like ligand-protein composites using chemical shift changes, selective line broadening, and nuclear Overhauser effects (NOE's). Studies were done to confirm that there was some weak binding interaction between PTH and compound (8).

#### Active Agents

##### Active Agents

Active agents suitable for use in the present invention include biologically active agents and chemically active agents, including, but not limited to, pesticides, pharmacological agents, and therapeutic agents.

For example, biologically or chemically active agents suitable for use in the present invention include, but are not limited to, proteins; polypeptides; peptides; hormones; polysaccharides, and particularly mixtures of muco-polysaccharides; carbohydrates; lipids; small polar organic molecules (*i.e.* polar organic molecules having a molecular weight of 500 daltons or less); other organic compounds; and particularly compounds which by themselves do not pass (or which pass only a fraction of the administered dose) through the gastro-intestinal mucosa and/or are susceptible to chemical cleavage by acids and enzymes in the gastro-intestinal tract and/or are rendered less active or inactive; or any combination thereof.

Further examples include, but are not limited to, the following, including synthetic, natural or recombinant sources thereof: growth hormones, including human growth hormones (hGH), recombinant human growth hormones (rhGH), bovine growth hormones, and porcine growth hormones; growth hormone releasing hormones; growth hormone releasing factor, interferons, including  $\alpha$ ,  $\beta$  and  $\gamma$ , interleukin-1; interleukin-2;

insulin, including porcine, bovine, human, and human recombinant, optionally having counter ions including zinc, sodium, calcium and ammonium; insulin-like growth factor, including IGF-1; heparin, including unfractionated heparin, heparinoids, dermatans, chondroitins, low molecular weight heparin, very low molecular weight heparin and ultra low molecular weight heparin; calcitonin, including salmon, eel, porcine and human; erythropoietin; atrial natriuretic factor; antigens; monoclonal antibodies; somatostatin; protease inhibitors; adrenocorticotropin, gonadotropin releasing hormone; oxytocin; leutinizing-hormone-releasing-hormone; follicle stimulating hormone; glucocerebrosidase; thrombopoietin; filgrastim; prostaglandins; cyclosporin; vasopressin; cromolyn sodium (sodium or disodium chromoglycate); vancomycin; desferrioxamine (DFO); bisphosphonates, including alendronate, tiludronate, etidronate, clodronate, pamidronate, olpadronate, and incadronate; parathyroid hormone (PTH), including its fragments; antimicrobials, including antibiotics, anti-bacterials and anti-fungal agents; vitamins; analogs, fragments, mimetics or polyethylene glycol (PEG)-modified derivatives of these compounds; or any combination thereof. Non-limiting examples of antibiotics include gram-positive acting, bacteriocidal, lipopeptidal and cyclic peptidal antibiotics, such as daptomycin and analogs thereof.

#### **Delivery systems**

The composition of the present invention comprises one or more delivery agent compounds of the present invention, and one or more active agents. In one embodiment, one or more of the delivery agent compounds, or salts of these compounds, or poly amino acids or peptides of which these compounds or salts form one or more of the units thereof, may be used as a delivery agent by mixing with the active agent prior to administration to form an administration composition.

The administration compositions may be in the form of a liquid. The solution medium may be water, 25% aqueous propylene glycol and phosphate buffer. Other dosing vehicles include polyethylene glycol. Dosing solutions may be prepared by mixing a solution of the delivery agent compound with a solution of the PTH, just prior to administration. Alternately, a solution of the delivery agent compound (or PTH) may be mixed with the solid form of the PTH (or delivery agent compound). The delivery



agent compound and the PTH may also be mixed as dry powders. The delivery agent compound and the active agent can also be admixed during the manufacturing process.

The dosing solutions may optionally contain additives such as phosphate buffer salts, citric acid, glycols, or other dispersing agents. Stabilizing additives may be  
5 incorporated into the solution, preferably at a concentration ranging between about 0.1 and 20% (w/v).

The administration compositions may alternately be in the form of a solid, such as a tablet, capsule or particle, such as a powder or sachet. Solid dosage forms may be prepared by mixing the solid form of the compound with the solid form of the active  
10 agent. Alternately, a solid may be obtained from a solution of compound and active agent by methods known in the art, such as freeze-drying (lyophilization), precipitation, crystallization and solid dispersion.

The administration compositions of the present invention may also include one or more enzyme inhibitors. Such enzyme inhibitors include, but are not limited to,  
15 compounds such as actinonin or epiactinonin and derivatives thereof. Other enzyme inhibitors include, but are not limited to, aprotinin (Trasylol) and Bowman-Birk inhibitor.

The amount of active agent used in an administration composition of the present invention is an amount effective to accomplish the purpose of the particular active agent for the target indication. The amount of active agent in the compositions typically is a  
20 pharmacologically, biologically, therapeutically, or chemically effective amount. However, the amount can be less than that amount when the composition is used in a dosage unit form because the dosage unit form may contain a plurality of delivery agent compound/ active agents compositions or may contain a divided pharmacologically, biologically, therapeutically, or chemically effective amount. The total effective amount  
25 can then be administered in cumulative units containing, in total, an effective amount of the active agent

The total amount of active agent to be used can be determined by methods known to those skilled in the art. However, because the compositions of the invention may deliver active agent more efficiently than compositions containing the active agent alone,  
30 lower amounts of biologically or chemically active active agent than those used in prior

dosage unit forms or delivery systems can be administered to the subject, while still achieving the same blood levels and/or therapeutic effects.

The presently disclosed delivery agent compounds facilitate the delivery of biologically active agent, particularly in oral, intranasal, sublingual, intraduodenal, subcutaneous, buccal, rectal, vaginal, mucosal, pulmonary, transdermal, intradermal, parenteral, intravenous, intramuscular and ocular systems, as well as traversing the blood-brain barrier.

Dosage unit forms can also include any one or combination of excipients, diluents, disintegrants, lubricants, plasticizers, colorants, flavorants, taste-masking agents, sugars, sweeteners, salts, and dosing vehicles, including, but not limited to, water, 1,2-propane diol, ethanol, olive oil, or any combination thereof. The presently disclosed delivery agent compounds facilitate the delivery of biologically and chemically active agents, particularly in oral, intranasal, sublingual, intraduodenal, subcutaneous, buccal, intracolonic, rectal, vaginal, mucosal, pulmonary, transdermal, intradermal, parenteral, intravenous, intramuscular and ocular systems, as well as traversing the blood-brain barrier.

Dosage unit forms can also include any one or combination of excipients, diluents, disintegrants, lubricants, plasticizers, colorants, flavorants, taste-masking agents, sugars, sweeteners, salts, and dosing vehicles, including, but not limited to, water, 1,2-propane diol, ethanol, olive oil, or any combination thereof.

The compounds and compositions of the subject invention are useful for administering biologically active agent to any animal, including but not limited to birds such as chickens; mammals, such as rodents, cows, pigs, dogs, cats, primates, and particularly humans; and insects. The system is particularly advantageous for delivering biologically active agent that would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone (i.e. the area in which the active agent of the delivery composition is to be released) and within the body of the animal to which they are administered. Particularly, the compounds and compositions of the present invention are useful in orally administering active agent, especially those that are not ordinarily orally deliverable, or those for which improved delivery is desired.

The compositions comprising the compounds and active agent have utility in the delivery of active agent to selected biological systems and in an increased or improved bioavailability of the active agent compared to administration of the active agent without the delivery agent. Delivery can be improved by delivering more active agent over a period of time, or in delivering active agent in a particular time period (such as to effect quicker or delayed delivery), or in delivering the active agent at a specific time, or over a period of time (such as sustained delivery).

Another embodiment of the present invention is a method for the treatment or prevention of a disease or for achieving a desired physiological effect, such as those listed in the table below, in an animal by administering the composition of the present invention. Specific indications for active agents can be found in the Physicians' Desk Reference (54<sup>th</sup> Ed., 2000, Medical Economics Company, Inc., Montvale, NJ), which is herein incorporated by reference. The active agents in the table below include their analogs, fragments, mimetics, and polyethylene glycol-modified derivatives.

Active Agent	Disease and Physiological Effect
Growth hormones	Growth disorders
Interferons, including $\alpha$ , $\beta$ and $\gamma$ .	Viral infection, including chronic cancer and multiple sclerosis
Interleukin-1; interleukin-2.	Viral infection; cancer
Insulin; Insulin-like growth factor IGF-1.	Diabetes
Glucagon-like Peptides (GLP) and GLP-agonists and antagonists	Insulin and eating disorders - regulate blood glucose via stimulation of glucose-dependent insulin secretion, inhibition of gastric emptying, and inhibition of glucagon secretion; may also regulate glycogen synthesis in adipose tissue and muscle.
Heparin	Thrombosis; prevention of blood coagulation
Calcitonin.	Osteoporosis; diseases of the bone
Erythropoietin	Anemia
Atrial naturetic factor	Vasodilation
Antigens	Infection
Monoclonal antibodies	To prevent graft rejection; cancer
Somatostatin	Bleeding ulcer; erosive gastritis
Protease inhibitors	AIDS
Adrenocorticotropin	High cholesterol (to lower cholesterol)
Gonadotropin releasing hormone	Ovulatory dysfunction (to stimulate ovulation)
Oxytocin	Labor disfunction (to stimulate contractions)

Active Agent	Disease and Physiological Effect
Leutinizing-hormone-releasing-hormone; follicle stimulating hormone	Regulate reproductive function
Glucocerebrosidase	Gaucher disease (to metabolize lipoprotein)
Thrombopoietin	Thrombocytopenia
Filgrastim	Reduce infection in chemotherapy patients
Prostaglandins	Hypertension
Cyclosporin	Transplant rejection
Vasopressin	Bed-wetting; antidiuretic
Cromolyn sodium; Vancomycin	Asthma; allergies
Desferrioxamine (DFO)	Iron overload
Parathyroid hormone (PTH), including its fragments.	Osteoporosis; Diseases of the bone
Antimicrobials	Infection including gram-positive bacterial infection
Vitamins	Vitamin deficiencies
Bisphosphonates	Osteoporosis; Paget's disease; Inhibits osteoclasts

For example, one embodiment of the present invention is a method for treating a patient suffering from or susceptible to diabetes by administering insulin and at least one of the delivery agent compounds of the present invention.

- 5        Following administration, the active agent present in the composition or dosage unit form is taken up into the circulation. The bioavailability of the agent is readily assessed by measuring a known pharmacological activity in blood, e.g. an increase in blood clotting time caused by heparin, or a decrease in circulating calcium levels caused by calcitonin. Alternately, the circulating levels of the active agent itself can be
- 10        measured directly.

### **Examples**

The following examples illustrate the invention without limitation. All parts are given by weight unless otherwise indicated.

- 15        Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) analyses for the compounds listed below were conducted on a 300 MHz Bruker spectrometer using dimethyl sulfoxide (DMSO- $d_6$ ) as the solvent unless otherwise indicated

**Example 1 – Compound Preparation****Preparation of Compound 1**

A 1 L round bottom flask fitted with a magnetic stirrer is charged with 8-aminononanoic acid (1.17 equiv.) and 2 M aqueous sodium hydroxide (300 mL). 4-hydroxybenzoyl chloride (1.00 equiv.) is added portionwise over 1 hour to the stirred solution. After the addition, the reaction is stirred for 2.5 hours at ambient temperature, and the pH of the solution is kept at around 10 by the addition of 10 M sodium hydroxide. The solution is then acidified with 1 M hydrochloric acid (3.times.100 mL), water (100 mL), and air dried. It is redissolved in boiling acetone (around 500 mL), decolorized with activated charcoal (3 g), and filtered. Water (1.5 L) is added to the filtrate to induce the formation of a brown oil. The brown oil will solidify upon stirring at room temperature for 10 minutes. The crude solid is collected by filtration and recrystallized from methanol-water system to afford 9-(4-hydroxy-benzoylamino)-nonanoic acid.

**Example 2 - Parathyroid Hormone Delivery (PTH 1-34) Oral/ Intracolonic Delivery**

Oral gavage (PO) and/or intracolonic (IC) dosing solutions of delivery agent compound and human parathyroid hormone residues 1-34 (PTH) in water are prepared. A solution of the compound is made either with the sodium salt of the compound or by converting the free acid to its sodium salt. Typically, a solution of the compound is prepared in water and stirred, adding one equivalent of sodium hydroxide (1.0 N) when making sodium salt. The final dosing solutions are prepared by mixing the compound with a PTH stock solution (typically having a concentration of 5 mg PTH/ml) and diluting to the desired volume (usually 3.0 ml).

Male Sprague Dawley rats weighing 200 – 250 grams are fasted for 24 hours. Immediately prior to dosing, the rats are anesthetized with an intramuscular injection of ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) and then administered the dosing solution by oral gavage using an 11 cm Rusch 8 French catheter. The catheter is placed down the esophagus and the dosing solution are expressed slowly into the stomach. For screening studies, the dose of PTH is 200 mcg/kg, and the dose of delivery agent is 100

mg/kg. Blood samples are collected from the tail artery prior to dosing and at 15, 30, 45, minutes and 1, 1.5, 2, 2.5, and 3 hours after dosing. The serum is harvested and the samples assayed for PTH concentrations.

5 **Example 3**

**Salmon Calcitonin (sCT) Oral Delivery**

Oral dosing (PO) compositions of delivery agent compound and salmon calcitonin (sCT) in water are prepared. Typically 450 mg of compound are added to 2.0 mL of water. Either the sodium salt of the compound or the free acid is converted to the sodium salt by stirring the resultant solution and adding one equivalent of sodium hydroxide (1.0 N) and diluting with water. The solution is vortexed, then heated (about 37° C) and sonicated. The pH is adjusted to about 7 (6.5 to 8.5) with NaOH or HCl. 90 µg sCT from a stock solution is added to the solution. Water is then added to bring the total volume to about 3.0 mL (varies depending on solubility of the delivery agent compound). The typical dosing and sampling protocols are as follows. Male Sprague-Dawley rats weighing between 200-250g are fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing. A dosing group of five rats are administered one of the dosing solutions. For oral dosing, an 11 cm Rusch 8 French catheter is adapted to a 1 mL syringe with a pipette tip. The syringe is filled with dosing solution by drawing the solution through the catheter, which is then wiped dry. The catheter is placed down the esophagus leaving 1 cm of tubing past the rat's incisors. Solution is administered by pressing the syringe plunger.

Blood samples are collected serially from the tail artery, typically at time = 0, 10, 20, 30, 60 and 90 minutes. Serum sCT is determined by testing with a EIA kit (Kit # EIAS-6003 from Peninsula Laboratories, Inc., San Carlos, CA) modifying the standard protocol from the kit as follows: incubated with 50 µl peptide antibody for 2 hours with shaking in the dark, washed the plate, added serum and biotinylated peptide and diluted with 4 mL buffer, and shake overnight in the dark. Numbers are adjusted according to baseline values obtained at time = 0.

30

**Example 4 Heparin Delivery Oral/Intracolonic Delivery**

Oral gavage (PO) and/or intracolonic (IC) dosing solutions containing a delivery agent compound and heparin sodium USP in 25% aqueous propylene glycol are prepared. Either the sodium salt of the compound is used or the free acid is converted to the sodium salt with one equivalent of sodium hydroxide. Typically, delivery agent compound and heparin (about 166-182 IU/mg) are mixed by vortex as dry powders. This dry mixture is dissolved in 25% v/v aqueous propylene glycol, vortexed and placed in a sonicator (about 37° C). The pH is adjusted to about 7 (6.5 to 8.5) with aqueous NaOH (2N). The dosing solution is sonicated to produce a clear solution. The final volume is adjusted to 3.0 mL.

The typical dosing and sampling protocols are as follows. Male Sprague-Dawley rats weighing between 275-350g are fasted for 24 hours and anesthetized with ketamine hydrochloride (88 mg/kg) intramuscularly immediately prior to dosing. A dosing group of five rats is administered one of the dosing solutions. For oral gavage (PO) dosing, an 11 cm Rusch 8 French catheter is adapted to a 1 mL syringe with a pipette tip. The syringe is filled with dosing solution by drawing the solution through the catheter, which is then wiped dry. The catheter is placed down the esophagus leaving 1 cm of tubing past the rat's incisors. Solution is administered by pressing the syringe plunger. For intracolonic (IC) dosing, a 7.5 cm 8 fr Rusch catheter is adapted to a 1 ml syringe with a pipette tip. The dosing catheter is inserted into the colon through the anus until the tube is no longer visible. The dosing solution is expressed slowly into the colon.

Citrated blood samples are collected by cardiac puncture following the administration of ketamine (88 mg/kg), typically at time – 0.25, 0.5, 1.0 and 1.5 hours. Heparin activity is determined by utilizing the activated partial thromboplastin time (APTT) according to the method of Henry, J.B., Clinical Diagnosis and Management by Laboratory Methods, Philadelphia, PA, W.B. Saunders (1979). Previous studies indicated baseline values of about 20 sec.

**Example 5****Recombinant Human Growth Hormone (rhGH) Oral/Intracolonic Delivery**

Oral gavage (PO) and/or intracolonic (IC) dosing solutions of delivery agent compound and rhGH in phosphate buffer are prepared. A solution of the compound is

made either with the sodium salt of the compound or by converting the free acid to its sodium salt. Typically, a solution of the compound is prepared in phosphate buffer and stirred, adding one equivalent of sodium hydroxide (1.0 N) when making sodium salt. The final dosing solutions are prepared by mixing the compound with an rhGH stock solution (15 mg rhGH/ml) and diluting to the desired volume (usually 3.0 ml). The typical dosing and sampling protocols are as follows. Male Sprague-Dawley rats weighing between 200-250g are fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing. A dosing group of five rats is administered one of the dosing solutions. For oral gavage (PO) dosing, an 11 cm Rusch 8 French catheter is adapted to a 1 mL syringe with a pipette tip. The syringe is filled with dosing solution by drawing the solution through the catheter, which is then wiped dry. The catheter is placed down the esophagus leaving 1 cm of tubing past the rat's incisors. Solution is administered by pressing the syringe plunger. For intracolonic (IC) dosing, a 7.5 cm Rusch catheter tube (French 8 or 6) is adapted to a syringe with an Eppendorf pipette tip. The syringe is filled with the dosing solution by drawing the solution through the catheter tube. The catheter tube is wiped dry. K-Y jelly is applied to the tip avoiding contact with the eye of the tube, and the tube is inserted into the colon through the anus until the tube is no longer visible. The solution is injected by pressing the syringe plunger, and the tube is removed.

Blood samples are collected serially from the tail artery, typically at time = 0, 15, 30, 45, 60 and 90 minutes for oral and 0, 10, 20, 30, 60 and 90 for IC dosing. The five samples from each time period are pooled. Serum rHGH concentrations are quantified by an rHGH immunoassay test kit (Kit #K1F4015 from Genzyme Corporation Inc., Cambridge, MA). Previous studies indicated baseline values of about zero.

### **Example 6**

#### **Interferon - Oral Delivery**

Dosing solutions of delivery agent compound and human interferon (IFN) were prepared in deionized water. The free acid of the delivery agent compound was converted to the sodium salt with one equivalent of sodium hydroxide. Typically, a solution of the delivery agent compound was prepared in water and stirred, adding one



equivalent of sodium hydroxide (1.0 N) when making the sodium salt. This mixture was vortexed and placed in a sonicator (about 37°C). The pH was adjusted to about 7.0 to 8.5 with aqueous NaOH. The mixture was vortexed to produce a uniform suspension or solution, also using sonication and heat if necessary. Additional NaOH was added, if  
5 necessary, to achieve uniform solubility, and the pH re-adjusted to about 7.0 to 8.5. The delivery agent compound solution was mixed with an IFN stock solution (about 22.0 to 27.5 mg/ml in phosphate buffered saline) and diluting to the desired volume (usually 3.0 ml). The final delivery agent compound and IFN doses, and the dose volumes are listed below in Table 7.

10 The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing and again as needed to maintain anesthesia. A dosing group of five animals was administered one of the dosing solutions. An 11 cm Rusch 8 French catheter was adapted to a 1 ml  
15 syringe with a pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the incisors. The dosing solution was administered by pressing the syringe plunger.

Blood samples were collected serially from the tail artery, typically at time = 0,  
20 15, 30, 45, 60 and 90 minutes. Serum IFN concentrations were quantified using Cytoscreen Immunoassay Kit for human IFN-alpha (catalog # KHC4012 from Biosource International, Camarillo, CA). Previous studies indicated baseline values of about zero. Results from the animals in each group were averaged for each time point.

#### 25 **Example 7 Insulin – Oral Delivery**

Oral dosing (PO) compositions of delivery agent compound and human zinc insulin (minimum 26 IU/mg available from Calbiochem – Novabiochem Corp, La Jolla, CA) were prepared in deionized water. Typically, 500 mg of delivery agent compound was added to 1.5 ml of water. The free acid of the delivery agent compound was  
30 converted to the sodium salt by stirring the resultant solution and adding one equivalent of sodium hydroxide. The solution was vortexed, then heated (about 37°C) and

sonicated. The pH was adjusted to about 7 to 8.5 with NaOH or HCl. Additional NaOH was added, if necessary, to achieve uniform solubility, and the pH re-adjusted to about 7 to 8.5. Water was then added to bring the total volume to about 2.4 ml and vortexed. About 1.25 mg insulin from an insulin stock solution (15 mg/ml made from 0.5409 g  
5 insulin and 18 ml deionized water, adjusting with HCl and NaOH to pH 8.15 and to obtain a clear solution using 40 ml concentrated HCl, 25 ml 10N NaOH and 50 ml 1N NaOH) was added to the solution and mixed by inverting. The solution may be used in the dosing protocol immediately, or alternatively, the solution may be placed into a 37°C water bath for one hour prior to dosing. The final delivery agent compound dose, insulin  
10 dose and dose volume amounts are listed below in Table 8.

The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between about 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing and again as needed to maintain anesthesia. A dosing group of five animals was administered  
15 one of the dosing solutions. For oral dosing, an 11 cm Rusch 8 French catheter was adapted to a 1 ml syringe with a pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the incisors. The dosing solution was administered by pressing the syringe plunger.

20 Blood samples were collected serially from the tail artery, typically at time = 15, 30, 60, 120 and 180 minutes. Serum insulin levels were determined with an Insulin ELISA Test Kit (Kit # DSL-10-1600 from Diagnostic Systems Laboratories, Inc., Webster, TX), modifying the standard protocol in order to optimize the sensitivity and linear range of the standard curve for the volumes and concentrations of the samples used  
25 in the present protocol. Serum human insulin concentrations ( $\mu$ U/ml) were measured for each time point for each of the five animals in each dosing group. The five values for each time point were averaged and the results plotted as serum insulin concentration versus time. (Previous experiments revealed no measurable levels of human insulin following oral dosing with human insulin alone.)

30

**Example 8: Insulin - Pulmonary Delivery**

Dosing compositions of delivery agent compound and human insulin in water were prepared. Typically, to 1.5 mg of delivery agent compound was added deionized water to bring the volume to 1.0 ml, and the solution was vortexed. Either the sodium salt of the delivery agent compound was used or the free acid was converted to the sodium salt by stirring the resultant solution and adding one equivalent of sodium hydroxide (10 N) and diluting with water. The solution was vortexed, then heated (about 37°C) and sonicated. The pH was adjusted to between about 7.0 to 8.5 with NaOH or HCl. 75 µl human insulin stock solution (2 mg/ml) was added to the solution. (The stock solution was made as follows. To 0.02 g insulin was added 3 ml pH 3.0 HCl solution in deionized water. The pH of the resulting solution was brought to below 3.0 (about 2.6) with HCl and NaOH until the solution was clear. The pH was then raised to 7.6 using NaOH and HCl. The final volume was brought to 10 ml with pH 7.5 deionized water. Final pH 7.59.) Water was then added to bring the total volume to 2.0 ml, and the solution was inverted gently several times. The solution may be used in the dosing protocol immediately, or alternatively, the solution may be placed into a 37°C water bath for one hour prior to dosing. The final delivery agent compound dose, insulin dose and volume dose amounts are listed below in Table 9.

The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (3.0 mg/kg) 15 minutes prior to dosing and again as needed to maintain anesthesia (using the same amount of ketamine and 1.5 mg/kg chlorpromazine). Typically, a dosing group of five animals was administered one of the dosing solutions. A control group of five animals was dosed insulin alone. A tracheal instillator for rodents, equipped with light (available from Penn Century, Inc., Pittsburgh, PA) was filled with dosing solution and inserted down the throat until the needle went into the trachea (confirmed visually). The dosing solution was administered by pressing the plunger.

Blood samples from each animal were collected serially from the tail artery, typically at 5, 15, 30, 60 and 120 minutes after dosing. Serum insulin levels were determined with an Insulin ELISA Test Kit (Kit # DSL-10-1600 from Diagnostic

Systems Laboratories, Inc., Webster, TX), modifying the standard protocol in order to optimize the sensitivity and linear range of the standard curve for the volumes and concentrations of the samples used in the present protocol. Serum insulin concentrations ( $\mu\text{U/ml}$ ) were measured for each time point for each of the five animals in each dosing group. The five values for each time point were averaged and the results plotted as serum insulin concentration versus time. The ratio of the area under the curve (AUC) for the test group versus that of the control group is reported below. The ratio of the maximum serum insulin concentration ( $C_{\text{max}}$ ) for the test group versus that of the control group is also reported below.

10        The above mentioned patents, applications, test methods, and publications are hereby incorporated by reference in their entirety.

#### **Example 9 - Cromolyn - Oral Delivery**

Dosing solutions containing a delivery agent compound (prepared as in Example 1) and cromolyn, disodium salt (cromolyn)(from Sigma Chemical Co., St. Louis, MO) were prepared in deionized water. The free acid of the delivery agent compound was converted to the sodium salt with one equivalent of sodium hydroxide. This mixture was vortexed and placed in a sonicator (about  $37^{\circ}\text{C}$ ). The pH was adjusted to about 7-7.5 with aqueous NaOH. Additional NaOH was added, if necessary, to achieve uniform solubility, and the pH re-adjusted. The mixture was vortexed to produce a uniform solution, also using sonication and heat if necessary. The delivery agent compound solution was mixed with cromolyn from a stock solution (175 mg cromolyn/ml in deionized water, pH adjusted, if necessary, with NaOH or HCl to about 7.0, stock solution stored frozen wrapped in foil, then thawed and heated to about  $30^{\circ}\text{C}$  before using). The mixture was vortexed to produce a uniform solution, also using sonication and heat if necessary. The pH was adjusted to about 7-8 with aqueous NaOH. The solution was then diluted with water to the desired volume (usually 2.0 ml) and concentration and stored wrapped in foil before use. The final delivery agent compound and cromolyn doses, and the dose volumes are listed below in Table 10.

30    The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and were anesthetized with

ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing and again as needed to maintain anesthesia. A dosing group of five animals was administered one of the dosing solutions. An 11cm Rusch 8 French catheter was adapted to a 1 ml syringe with a pipette tip. The syringe was filled with dosing solution by drawing the  
5 solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the incisors. The dosing solution was administered by pressing the syringe plunger.

Blood samples were collected via the tail artery, typically at 0.25, 0.5, 1.0 and 1.5 hours after dosing. Serum cromolyn concentrations were measured by HPLC. Samples  
10 were prepared as follows: 100  $\mu$ l serum was combined with 100  $\mu$ l 3N HCl and 300  $\mu$ l ethyl acetate in an eppendorf tube. The tube was vortexed for 10 minutes and then centrifuged for 10 minutes at 10,000 rpm. 200  $\mu$ l ethyl acetate layer was transferred to an eppendorf tube containing 67  $\mu$ l 0.1 M phosphate buffer. The tube was vortexed for 10 minutes and then centrifuged for 10 minutes at 10,000 rpm. The phosphate buffer layer  
15 was then transferred to an HPLC vial and injected into the HPLC (column = Keystone Exsil Amino 150x2 mm i.d., 5  $\mu$ m, 100Å; mobile phase = 35% buffer(68 mM  $\text{KH}_2\text{PO}_4$  adjusted to pH 3.0 with 85%  $\text{H}_3\text{PO}_4$ )/65% acetonitrile; injection volume = 10  $\mu$ l; flow rate = 0.30 ml/minute; cromolyn retention time = 5.5 minutes; absorbance detected at 240 nm). Previous studies indicated baseline values of about zero

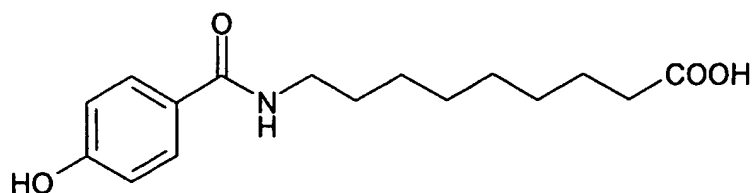
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**WHAT IS CLAIMED IS:**

1. A compound having the formula:



and salts thereof.

5

2. A composition comprising:
  - (A) an active agent; and
  - (B) the compound of claim 1, and mixtures thereof.

3. The composition of claim 2, wherein the active agent is selected from the group consisting of a biologically active agent, a chemically active agent, and a combination thereof.

4. The composition of claim 3, wherein the biologically active agent comprises at least one protein, polypeptide, peptide, hormone, polysaccharide, mucopolysaccharide, carbohydrate, or lipid.

5. The composition of claim 3, wherein the biologically active agent is selected from the group consisting of: growth hormones, human growth hormones recombinant human growth hormones (rhGH), bovine growth hormones, porcine growth hormones, growth hormone releasing hormones, growth hormone releasing factor, interferons,  $\alpha$ -interferon,  $\beta$ -interferon,  $\gamma$ -interferon, interleukin-1, interleukin-2, insulin, porcine insulin, bovine insulin, human insulin, human recombinant insulin, insulin-like growth factor (IGF), IGF-1, heparin, unfractionated heparin, heparinoids, dermatans, chondroitins, low molecular weight heparin, very low molecular weight heparin, ultra low molecular weight heparin, calcitonin, salmon calcitonin, eel calcitonin, human calcitonin; erythropoietin (EPO), atrial natriuretic factor, antigens, monoclonal antibodies,

somatostatin, protease inhibitors, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, leutinizing-hormone-releasing-hormone, follicle stimulating hormone, glucocerebrosidase, thrombopoeitin, filgrastim, postaglandins, cyclosporin, vasopressin, cromolyn sodium, sodium chromoglycate, disodium chromoglycate, vancomycin, desferrioxamine (DFO), parathyroid hormone (PTH), fragments of PTH, antimicrobials, anti-fungal agents, vitamins; analogs, fragments, mimetics and polyethylene glycol (PEG)-modified derivatives of these compounds; and any combination thereof.

10        6.            The composition of claim 3, wherein the biologically active agent comprises insulin, heparin, calcitonin, parathyroid hormone, erythropoietin, growth hormones or combinations thereof.

15        7.            The composition of claim 3, wherein the biologically active agent comprises recombinant human growth hormones.

8.        The composition of claim 3, wherein the biologically active agent comprises parathyroid hormone.

20        9.            The composition of claim 3, wherein the biologically active agent comprises insulin.

10.       The composition of claim 3, wherein the biologically active agent comprises heparin.

25

11.       The composition of claim 3, wherein the biologically active agent comprises calcitonin.

30        12.           The composition of claim 3, wherein the biologically active agent comprises interferon.

13. A composition comprising:
- (A) an active agent; and
  - (B) a poly(amino acid) comprising a compound having a formula selected from the group consisting of the compounds of claim 1,  
5 salts thereof and mixtures thereof.
14. The composition of claim 13 wherein the poly (amino acid) is a polypeptide.
15. A dosage unit form comprising:
- (A) the composition of claim 2; and
  - (B)
    - (a) an excipient
    - (b) a diluent
    - (c) a disintegrant,
    - 15 (d) a lubricant,
    - (e) a plasticizer,
    - (f) a colorant,
    - (g) a dosing vehicle, or
    - (h) any combination thereof.
16. The dosage unit form of claim 15, wherein the active agent is selected from the group consisting of a biologically active agent, a chemically active agent, and a combination thereof.
17. The dosage unit form of claim 16, wherein the biologically active agent comprises at least one protein, polypeptide, peptide, hormone, polysaccharide, mucopolysaccharide, carbohydrate, or lipid.
18. The dosage unit form of claim 16, wherein the biologically active agent is  
30 selected from the group consisting of:  
growth hormones, human growth hormones (hGH), recombinant human growth



hormones (rhGH), bovine growth hormones, porcine growth hormones, growth hormone releasing hormones, growth hormone releasing factor, interferons,  $\alpha$ -interferon,  $\beta$ -interferon,  $\gamma$ -interferon, interleukin-1, interleukin-2, insulin, porcine insulin, bovine insulin, human insulin, human recombinant insulin, insulin-like growth factor, insulin-like growth factor-1, heparin, unfractionated heparin, heparinoids, dermatans, chondroitins, low molecular weight heparin, very low molecular weight heparin, ultra low molecular weight heparin, calcitonin, salmon calcitonin, eel calcitonin, human calcitonin; erythropoietin, atrial natriuretic factor, antigens, monoclonal antibodies, somatostatin, protease inhibitors, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, leutinizing-hormone-releasing-hormone, follicle stimulating hormone, glucocerebrosidase, thrombopoietin, filgrastim, prostaglandins, cyclosporin, vasopressin, cromolyn sodium, sodium chromoglycate, disodium chromoglycate, vancomycin, desferrioxamine, parathyroid hormone, fragments of PTH, antimicrobials, antifungal agents, vitamins; analogs, fragments, mimetics and polyethylene glycol-modified derivatives of these compounds; and any combination thereof.

19. The dosage unit form of claim 16, wherein the biologically active agent comprises insulin, heparin, calcitonin, parathyroid hormone, erythropoietin, human growth hormones or combinations thereof.

20. The dosage unit form of claim 15, wherein the active agent comprises recombinant human growth hormone.

21. The dosage unit form of claim 15, wherein the active agent comprises parathyroid hormone.

22. The dosage unit form of claim 15, wherein the active agent comprises insulin.

23. The dosage unit form of claim 15, wherein the active agent comprises

heparin.

24. The dosage unit form of claim 15, wherein the active agent comprises calcitonin.

5

25. The dosage unit form of claim 15, wherein the active agent comprises interferon.

10

26. The dosage unit form of claim 15, wherein the dosage unit form comprises a dosing vehicle comprising a tablet, a capsule, a powder, or a liquid.

27. The dosage unit form of claim 15, wherein the dosing vehicle is liquid selected from the group consisting of water, 1,2-propane diol, ethanol, and any combination

15

28. A method for administering a biologically-active agent to an animal in need of the agent, the method comprising administering orally to the animal the composition of claim 3.

20

29. A method for preparing a composition comprising mixing:  
(A) at least one active agent;  
(B) the compound of claim 1; and  
(C) optionally, a dosing vehicle.

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(54) Title: COMPOUND AND COMPOSITION FOR DELIVERING ACTIVE AGENTS

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EAST

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,990,166 A (LEONE-BAY et al.) 23 November 1999. See entire document.	1-29

☐ Further documents are listed in the continuation of Box C.

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